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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/546,573	04/10/00	HOLTEN-ANDERSEN	M	19829-000300

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EXAMINER	
RAWLINGS,S	
ART UNIT	**PAPER NUMBER**
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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Office Action Summary	Application No. 09/546,573	Applicant(s) HOLTEN-ANDERSEN ET AL.	
	Examiner Stephen L. Rawlings, Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence addr ss --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *6-12 and 20-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,13-19 and 27-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-37* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,8, 9 1/2*
4) ☒ Interview Summary (PTO-413) Paper No(s). *10* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

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DETAILED ACTION

1. The election filed on June 8, 2001 in Paper No. 7 is acknowledged and has been entered.

2. Claims 1-37 are pending in the application. Claims 6-12 and 20-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 7.

3. Claims 1-5, 13-19, and 27-37 are currently under prosecution.

Election/Restrictions

4. Applicant's election with traverse of Group I, claims 1-5, 13-19, 27, and 30-37 in Paper No. 7 is acknowledged. The traversal is on the ground(s) that (a) searching the invention of Group III together with the elected invention of Group I would not constitute serious burden on the examiner, (b) the inventions in each of the different groups are identically classified and are therefore not distinct, and (c) it is improper to require a restriction of the subject matter of a single claim.

With regard to Groups I and III, this traversal is found persuasive and accordingly the elected Group I and Group III are rejoined. For the same reason, Groups II and IV are necessarily rejoined. Claims 1-5, 13-19, and 27-37 in Groups I and III are now to be examined as being drawn to the elected invention.

With regard to the remaining groups, Applicants' arguments have not been found persuasive. The inventions of Group I / III and Group II / IV are distinct for the reason set forth in the previous Office Action (Paper No. 4). The search required for examination of Group I / III together with Group II / IV would constitute a serious burden, because the search required for both Groups I / III and Groups II / IV are not coextensive; different searches are required for examination of each group. Furthermore, classification of subject matter is only one indication of the burden of the

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search that is required for examination of an invention. In this particular art, the literature search is more relevant than a classification search and is, therefore, a better indication of the burdensome nature of the search that is required. With regard to claims 13, 14, and 27-37, which are commonly restricted to Groups I / III and II / IV, the claims recite limitations that are drawn to either invention in the alternative and it is, therefore, not always improper to restrict a single claim to more than one group. The requirement is still deemed proper and is therefore made FINAL.

Specification

5. The abstract of the disclosure is objected to because its placement in the specification is improper.

The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

The following order or arrangement is preferred in framing the specification and, except for the reference to "Microfiche Appendix" and the drawings, each of the lettered items should appear in upper case, without underlining or bold type, as section headings. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) Title of the Invention.

(b) Cross-References to Related Applications.

(c) Statement Regarding Federally Sponsored Research or Development.

(d) Reference to a "Microfiche Appendix" (see 37 CFR 1.96).

(e) Background of the Invention.

1. Field of the Invention.
2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.

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(f) Brief Summary of the Invention.

(g) Brief Description of the Several Views of the Drawing(s).

(h) Detailed Description of the Invention.

(i) Claim or Claims (commencing on a separate sheet).

(j) Abstract of the Disclosure (commencing on a separate sheet).

(k) Drawings.

(l) Sequence Listing (see 37 CFR 1.821-1.825).

Claim Objections

6. Claims 4, 5, 13, 14, 18, 19, and 27-37 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim and because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n). Accordingly, the claims 4, 5, 13, 14, 18, 19, and 27-37 have not been further treated on the merits.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-3 and 15-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method for determining whether an individual or a patient that has been treated for primary cancer is likely to have cancer or metastatic cancer, respectively. As broadly and reasonably interpreted, claims 1-3 encompass a method for assessing an individual's risk for developing primary or metastatic cancer (i.e., having primary or metastatic cancer in the future). Claims 15-17 encompass a

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method for assessing a patient's risk for developing metastatic cancer that may develop secondarily or independently of a primary cancer for which said individual was treated. Moreover, it is noted that together the claims encompass a method for determining an individual or patient's risk for developing *any* type of primary or metastatic cancer. Alternatively, the claims are reasonably interpreted to encompass a method for diagnosing the incidence of primary or metastatic cancer in an individual or the incidence of metastatic cancer in a patient treated for primary cancer, again, wherein said metastatic cancer may develop secondarily or independently of the primary cancer for which said individual was treated. Together the claims encompass a method for diagnosing *any* type of primary or metastatic cancer in an individual or a patient treated for primary cancer. The claims require the determination of a single parameter, wherein said parameter corresponds to the concentration of TIMP-1 in a sample of bodily fluid, including, but not limited to a sample of blood plasma, blood serum, urine, saliva, feces, urine, cerebrospinal fluid, and lacrimal and sudoriferous gland secretions (i.e., tears and sweat). The claims require that if the determined parameter (i.e., the concentration of TIMP-1 in a body fluid sample) is at or beyond a discriminating value, the individual or patient is highly likely to have cancer at present or in the future. According to the claims, the discriminating value is determined by measuring the parameter (i.e., the concentration of TIMP-1) in body fluid samples acquired from both a healthy and a diseased population. If, on the other hand, the determined parameter is not at or beyond the discriminating value, the individual or patient is unlikely to have cancer at present or in the future.

The specification teaches that the invention "relates to a test to be used to screen large populations for the occurrence of cancer" (page 1, lines 5 and 6), but also teaches, which may be used to screen an individual or an entire population (page 5, line 4). More particularly, the specification teaches that the invention is a "highly specific" method for "early identification of patients having colorectal cancer" (page 1, lines 7 and 8). The specification teaches that the "test is based on the measurement of tissue inhibitor of metalloproteinases type I (TIMP-1), in various body fluids, including plasma, serum, stool, and urine" (page 1, lines 13 and 14). The specification exemplifies a

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method for establishing and using an immunologic assay (i.e., ELISA) to measure TIMP-1 in body fluid, namely blood plasma acquired from individuals presumed to be healthy and disease-free or from individuals that had been positively diagnosed previously with either colorectal or breast cancer (see the Examples, pages 12-36). The specification teaches that plasma samples acquired from patients that had previously been diagnosed with colorectal cancer have higher concentrations of TIMP-1 than plasma sample acquired from individuals that were presumed to be healthy and disease-free at the time the sample was acquired (page 6, lines 13-28). More particularly, in Example 4, the specification teaches that the median value of the concentration of TIMP-1 measured in the plasma samples of patients previously diagnosed with colorectal cancer was 141.1 micrograms/liter, but that the values ranged from 53.7 to 788.7 (page 26, lines 2-24). The specification teaches that the median value of the concentration of TIMP-1 measured in the plasma samples of individuals presumed to be healthy and disease-free was 88.6 micrograms/liter and ranged from 51.0 to 156.2 (page 27, lines 1 and 2). Nevertheless, the specification teaches that the "discriminating value", which is loosely defined as the threshold value of the concentration of TIMP-1 that is used to discriminate between an individual that has cancer and an individual that is presumed not to have cancer, *ranges* from 50-160 micrograms/liter (page 5, lines 6-8). The specification discloses that the invention cannot be used to stage colorectal cancer (see, for example, page 26, lines 26-30). In fact, the specification teaches, the highest TIMP-1 levels were not restricted to those patients having been diagnosed with advanced disease. Furthermore, the specification teaches the concentration of free TIMP-1 (i.e., a TIMP-1 molecule that is not in complex with a metalloproteinase) lacks diagnostic value (Example 7) and therefore measuring free the concentration of free TIMP-1 cannot be used to determine the likelihood that an individual or patient has colorectal cancer. The specification teaches by exemplification that the method also cannot be used to determine the likelihood that an individual or patient has primary, non-malignant breast cancer (Example 10).

The teachings of the specification cannot be extrapolated to the enablement of the invention commensurate in scope with the claims. Accordingly, one skilled in the art

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cannot practice the invention with a reasonable expectation of success without first performing extensive and undue experimentation.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

Once again, it is noted the claims are drawn to a method for determining whether an individual or a patient presently has cancer or will have cancer. However, it is also noted that the specification does not exemplify the claimed method. None of the examples included in the specification teach that the use of the invention to determine the likelihood that an individual or a patient has or will have primary or metastatic cancer of any type. Moreover, there is no factual evidence of record that indicates that the concentration of TIMP-1 in a bodily fluid of an individual or patient correlates with the incidence of cancer in said individual or patient. Accordingly, in the absence of working exemplification, particularly in the absence of exemplification that is commensurate in scope with the claims, one skilled in the art would not accept the assertion the claimed method can be used to determine the likelihood that an individual or patient has or will have cancer. Furthermore, there is insufficient guidance in the specification to enable one skilled in the art to practice the claimed method with a reasonable expectation of success without first performing extensive and undue experimentation. For example, the threshold value of the concentration of TIMP-1 that can be used to discriminate the individual or patient that has primary or metastatic cancer from the individual or patient that is disease-free is not disclosed in the specification. Rather, it is noted that the specification discloses a range of values (i.e., 50-160 micrograms of TIMP-1 per liter), but the specification also indicates that this range of values will vary experimentally (page 5, lines 5, lines 8-10). In view of the examples, it is apparent that the concentration of TIMP-1 in samples acquired from different individuals varies

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considerably. On the basis of the results acquired from practicing the invention, if one were to use the range of "discriminating" values that is disclosed in the specification, one would necessarily conclude that each of the individuals known to have colorectal cancer do, in fact, have colorectal cancer, since each the concentration of TIMP-1 in each of the individual's samples was determined to be at least 50 microgram/liter. However, based upon an analysis of the data consistent with the teachings of the specification, one would also have wrongly concluded that each one of the individuals, who were reportedly healthy and disease-free, has colorectal cancer. Nevertheless, even if the concentration of TIMP-1 in a sample acquired from an individual were to be determined to be much greater than 156.2 micrograms/liter (i.e., the upper value of the range of the concentrations of TIMP-1 measured in healthy individuals), the skilled artisan cannot determine whether the individual is more or less likely than another to have cancer, because the specification does not teach the correlation between the concentration of TIMP-1 and the likelihood that an individual has cancer. For the invention to be practically useful, as the specification teaches, the invention must be used to diagnose cancer in a patient and accordingly intervene clinically or else to assess a patient's risk for developing cancer and intervene clinically. However, this use of the invention is not exemplified, as only individuals known to have or not to have cancer have been tested. Moreover, based only upon the teachings of the specification, one skilled in the art cannot predict whether the invention can or will ever be used practically in a clinical setting. Clearly, the high degree of variance in the values of the concentration of TIMP-1 would preclude an accurate and precise determination of the likelihood that an individual will have cancer and the use of the invention would result in a significant number of misdiagnoses or in a significant over- or under-estimate of an individual's risk for developing cancer.

In support of the conclusion that the specification is not enabling, Ward (*Developmental Oncology* **21**: 91-106, 1985) teaches that a number of tumor-associated markers are, in fact, diagnostically unreliable (see abstract). Even CA-125, one of the more reliably used biomarkers known in the art, is not always effective for rendering a diagnosis of every type of cancer, particularly ovarian cancer (see US Patent No.

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5,536,817 A; column 2, line 47 to column 3, line 2). Consistently, with regard to the use of TIMP-1 as a marker, Zhou, et al (*Cancer Epidemiology, Biomarkers and Prevention* **7**: 109-112, 1998) teach "analysis of TIMP-1 serum levels revealed significant increases in pancreatic cancer patients, but TIMP-1 by itself was inadequate as a serum marker for cancer" (abstract).

Furthermore, it is has become increasingly recognized in the art that the use of a single diagnostic biomarker of cancer may be ineffective, particularly for the diagnosis of differently staged cancer. A newsletter published in 1997 by the Genesis Group Associates, Inc. (*Genesis Report-Dx*, Vol. 6, No. 3) teaches:

> "What we realize about tumors now is that they may not express that one marker you might be testing for, depending on the stage.
>
> "Over a period of time, as tumors become more aggressive, they express more tumor markers. But if you rely on a single marker you might not be able to detect that a tumor marker is actually being expressed" (NLDB Accession No. 97:320100, © 2001 Gale Group, page 5).

With specific regard to the use of TIMP-1 as a marker, Oberg, et al (*Anticancer Research* **20**: 1085-1091, 2000) teach that analyses of the total concentration of TIMP-1 in serum samples acquired from colorectal patients reveal that TIMP-1 is of limited value for tumor staging and prognosis (abstract). Oberg, et al also teach that "wide, overlapping ranges" of concentrations are observed, which serves to preclude the usefulness of analyses of TIMP-1 and other measured factors. Furthermore, Michael, et al (*Journal of Clinical Oncology* **17**: 1802-1808, 1999) teach that in contrast to the premise for the usefulness of the invention, TIMP-1 is largely absent from small-cell lung cancer specimens and that *decreased* tumoral expression of TIMP-1 rather than increased expression has prognostic significance.

Additionally, Pohl et al (non-serial, meeting abstract, 3rd International Conference of the Mediterranean Society of Tumor Marker Oncology, 1994) teach:

> No individual tumor marker is expressed by all histological types of ovarian cancer; accordingly, the combined use of several markers may help to overcome this diagnostic insensitivity. However, given the rapid growth in the number of tumor markers to choose from, there is a pressing need to objectively select those marker panels which are most meaningful and cost-effective in clinical practice.

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Although Pohl, et al refers to ovarian cancer, the teachings are relevant to a consideration of any protein that might be used as a diagnostic marker of any type of cancer. Accordingly, it is reasonable to expect that TIMP-1 will not be expressed or over-expressed by all forms of any one type of cancer, including colon, rectal, and breast cancer. In support of this assertion, it is again noted that the specification teaches that TIMP-1 cannot be used to distinguish different histological forms of colorectal cancer. Additionally, the specification teaches that TIMP-1 cannot be used to mark primary breast cancer. More strikingly, however, Ikebe, et al (*Clinical and Experimental Metastasis* **17**: 315-323, 1999) teach that in contrast to the premise for the usefulness of the invention, higher concentrations of TIMP-1 are found in non-metastatic cancer than in metastatic cancer (abstract). Therefore, Ikebe, et al suggest that low levels of TIMP-1 and high levels of the metalloproteinases might more aptly mark oral squamous cell carcinoma. In other studies, it is revealed the vast majority of some types of tumors whether metastatic or not, are entirely devoid of TIMP-1 (see, for example, Arnold, et al, *Clinical Cancer Research* **5**: 4028-4033, 1999).

Jung, et al (*Clinica Chimica Acta* **254**: 97-100, 1996); Form PTO-1449 (Paper No. 5), citation AN) teach that not all bodily fluids can or should be sampled in order to measure the amount of TIMP-1 in the body of a patient. For example, Jung, et al teach that analyses of "serum samples are not suited for the use of TIMP-1 as a diagnostic marker" (page 97). Jung, et al also teach that samples acquired in heparin appear to have higher concentrations of TIMP-1 than samples acquired in EDTA from the same individual, but point out that it is unclear which value is to be considered the more accurate (page 99). The specification only teaches the use of plasma samples and then only plasma samples acquired in EDTA. Pohl, et al (cited supra) also teach that it is important to establish which analytical methods are best suited to the evaluation of multiple tumor marker measurements (see abstract). In this regard, it is noted that the specification provides exemplification of an ELISA, but does not teach any other method for measuring the concentration of TIMP-1 in a sample, such as zymography. On the basis of the teachings of Jung, et al and Pohl, et al it is unclear that the amount of guidance provided in the specification is insufficient to enable one skilled in the art to

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readily determine which bodily fluid should be sampled and which methods are best suited for measuring the concentration of TIMP-1 in those samples.

Ward, et al (cited supra) teaches that some markers are better suited for evaluating response to antitumor therapy (abstract). With particular regard to colorectal cancer, McKay, et al (*International Journal of Oncology* 17: 153-158, 2000) teach "a wide range of tumor response is seen amongst patients with the **same** stage of colorectal cancer, even with the use of uniform chemotherapy" (emphasis added) (abstract). McKay, et al conclude that TIMP-1 is not clearly associated with clinical response to chemotherapy (abstract). Accordingly, although not specifically claimed, it is unclear that the invention can be used to assess clinical response.

On the other hand, the specification does teach that the method can be used to diagnose cancer. However, the specific guidelines that might be used for analysis of the resultant data acquired by the measurement of the concentration of TIMP-1 in a sample are absent from the specification. Tockman, et al (*Cancer Research* **52**: 2711s-2718s, 1992) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to diagnosis of any type of cancer, including colorectal and breast cancer. Tockman, et al teach that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end-points, establish quantitative criteria for marker presence/absence, and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** can be used for population screening (emphasis added) (page 2713, column 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and link those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and

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subsequent acknowledged disease is the essence of a valid intermediate end-point marker (page 2714, column 1). Clearly, prior to the successful application of newly described markers, validation against acknowledged disease end-points must occur and the markers' predictive value must be confirmed in prospective population trials (page 2716, column 2).

In consideration of the need to first validate TIMP-1 as a marker before its clinical application, it is noted that the increased expression of TIMP-1 alone may not be pathologic. Therefore, the increased expression of TIMP-1 may not be diagnostic of cancer. Aoudjit, et al (*International Journal of Cancer* **82**: 743-747, 1999) teach that while TIMP-1 is over-expressed in experimental lymphoma, it seems that TIMP-1 may have a pathologic role in the progression of the cancer (abstract). In view of the teachings of Aoudjit, et al it seems that the expression of metalloproteinases may be more causative of tumor progression, or rather the resultant ratio of the levels of expression of metalloproteinases and tissue inhibitors of the metalloproteinases, such as TIMP-1. In fact, numerous studies suggest that the ratio of the levels of the metalloproteinases and TIMP-1 is probably more predictive of recurrence, metastasis, and survival than analysis of the level of TIMP-1 alone. For example, Berend, et al (*Journal of Bone and Joint Surgery, American Volume* **80**: 11-17, 1998) teach "patients who had recurrent disease had a significantly higher ($p < 0.003$) ratio of matrix metalloproteinase-1 to tissue inhibitor of metalloproteinase-1 [TIMP-1] (mean, 0.939; range 0.647 to 1.101) than the patients who were free of disease" (abstract). Accordingly, one skilled in the art might conclude that measuring both the concentrations of the metalloproteinases and TIMP-1 and determining the ratio thereof may have diagnostic and/or prognostic value, but it is doubtful that one would conclude that measuring the level of TIMP-1 alone would be as effective. It is noted, however, that the specification does not teach a method for diagnosing a patient or assessing a patient's prognosis by measuring the levels of both the metalloproteinases and their inhibitors. Nevertheless, based upon the known high level of unpredictability in the art, it is unclear that such a method could be used effectively in a clinical setting to effectively diagnose cancer in a patient.

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In view of the teachings of Tockman, et al (cited supra) one skilled in the art would not accept the assertion that the invention can be used to diagnose any type of cancer, including colorectal and breast cancer. Moreover, in view of the teachings of Aoudjit, et al (cited supra) one skilled in the art would not accept the assertion that the invention can be used to assess an individual's risk for developing cancer, because the role of TIMP-1 over-expression in pathogenesis and the etiology of cancer is still not complete. In view of the teachings of Tockman, et al and Aoudjit, et al, the skilled artisan cannot predict whether the claimed invention will ever be practically useful in a clinical setting without first performing extensive and undue experimentation. In view of the teachings of Jung, et al and Pohl, et al, the level of guidance provided in the specification is insufficient to enable one skilled in the art to measure the concentration of TIMP-1 in a biologic sample, let alone to use the invention to render a definitive, differential diagnosis of any type of cancer. In view of the teachings of the other references cited above, it is certainly clear that one skilled in the art cannot practice the invention commensurate in scope with the claims with a reasonable expectation of success. Accordingly, one skilled in the art would have to perform extensive and undue experimentation, first to validate the use of the marker and then to assess its predictive value.

In summary, with regard to the usefulness of measuring TIMP-1 in the plasma of patients, Holten-Andersen, et al (*Clinical Cancer Research* **6**: 4292-4299, 2000) conclude, "Additional studies are needed to validate the clinical usefulness of plasma TIMP-1 measurements" (abstract).

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-3 and 15-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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Claims 1-3 and 15-17 are vague and indefinite because claim 1 and 15, respectively, recite the phrases "a method for determining whether an individual is likely to have cancer" or "a method for determining whether a patient who has been treated for primary cancer is likely to have metastatic cancer". The use of the phrases renders the claims vague and indefinite, because even in view of the specification, it cannot be determined whether the claims are drawn to a method for determining the probability that said individual or said patient will develop primary or secondary, metastatic cancer or to a method for determining if said individual or said patient already has primary or secondary, metastatic cancer. In other words, it is unclear whether Applicants' considers the invention to be a method for assessing an individual's risk for developing primary or secondary cancer (i.e., the likelihood that said individual will have cancer in the future) or a method for diagnosing pre-existent primary or secondary cancer in an individual (i.e., the likelihood that said individual currently has cancer). Furthermore, with regard to claim 15, it is unclear whether the claim requires the patient to have been treated successfully or unsuccessfully for primary cancer and accordingly it is unclear whether the claim requires the patient to be likely of having metastatic cancer that developed secondarily to the primary cancer or independently. Accordingly, one of ordinary skill in the art would not reasonably be apprised of the metes and bounds of the invention.

Claims 1-3 and 15-17 are also vague and indefinite because claims 1 and 15 recite the phrase "a first parameter representing the concentration of TIMP-1". The use of the phrase renders the claims vague and indefinite because it is unclear whether the claims require the first parameter to be equal to the concentration of TIMP-1 or to merely "represent" (i.e., correspond to) the concentration of TIMP-1. Accordingly, one of ordinary skill in the art would not reasonably be apprised of the metes and bounds of the invention.

Claims 1-3 and 15-17 are also vague and indefinite because the term "high" in claims 1 and 15 is a relative term that renders the claims indefinite. The term "high" is not defined by the claim and the specification does not provide a standard for ascertaining the requisite degree. Therefore, it cannot be determined just how likely it is

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that an individual or a patient will have primary or metastatic cancer now or in the future if the parameter is at or beyond a discriminating value. Therefore, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claims 1-3 and 15-17 are also vague and indefinite because claims 1 and 15 recite the phrase "a discriminating value". The use of the phrase renders the claims vague and indefinite because it is unclear what value of a first parameter is discriminating. Moreover, it is unclear how the value is discriminating. Accordingly, one of ordinary skill in the art would not reasonably be apprised of the metes and bounds of the invention.

Claims 1-3 and 15-17 are also vague and indefinite because claims 1 and 15 recite the phrase "the concentration of TIMP-1 in body fluid samples". Alone the phrase "the concentration of TIMP-1 in body fluid samples" would be interpreted to mean the total concentration of TIMP-1 in a sample. However, it is noted that claims 2 and 16, which depend from claims 1 and 15, respectively, recite the limitation "wherein the first parameter is the total concentration of TIMP-1". In view of the limitation in claims 2 and 16, the use of the phrase "the concentration of TIMP-1 in body fluid samples" renders claim 1 and 15 vague and indefinite because it is unclear whether the claims require the total concentration or merely part of the total concentration of TIMP-1 in the sample to be determined. Accordingly, one of ordinary skill in the art would not reasonably be apprised of the metes and bounds of the invention.

Claims 1-3 and 15-17 are also vague and indefinite because claims 1 and 15 recite the phrase "in body fluid samples". The use of the phrase renders the claims vague and indefinite because it is unclear whether the claims require the body fluid samples to be acquired from sampling the body fluids of the individual or the patient of line 1 in the claims or from sampling the body fluids of a different individual or patient or population of individuals or patients. Accordingly, one of ordinary skill in the art would not reasonably be apprised of the metes and bounds of the invention.

Claims 1-3 and 15-17 are indefinite because claims 1 and 15 do not recite a positive correlation step that clearly relates the method steps recited in the body of the claim to the preamble of the claim. Accordingly, one of ordinary skill in the art is not

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reasonably apprised of the metes and bounds of the invention. Amending claims 1 and 15 to recite the phrase "whereby the likelihood that said individual (patient) will have cancer is determined" after "value" in the last line can obviate this rejection.

Claims 3 and 17 are indefinite because claims 3 and 17 recite the limitation "said at least one first parameter" in line 2. There is insufficient antecedent basis for this limitation in the preamble of the claim or in the claim(s) from which claims 3 and 17 depend.

Claims 3 and 17 are vague and indefinite because claims 3 and 17 recite the term "thereby determining the discriminating value" in lines 3 and 4. The use of the term renders the claims vague and indefinite because it is unclear whether the "discriminating value" of line 4 is the same as the "discriminating value" of line 1. Accordingly, one of ordinary skill in the art would not reasonably be apprised of the metes and bounds of the invention. Also, if the discriminating values of lines 1 and 4 are different, there is insufficient antecedent basis for the limitation "the discriminating value" in line 4 of the claims.

Claims 3 and 17 are vague and indefinite because claims 3 and 17 recite the phrase "a predetermined specificity or a predetermined sensitivity". The use of the phrase renders the claims vague and indefinite because it is unclear to what level of a specificity or sensitivity the claims refer. It is also unclear whether the claims require the "discriminating value" of line 4 to identify the cancer population accurately or inaccurately or precisely or imprecisely. Moreover, it is unclear how the level of specificity or sensitivity is to be pre-determined. Accordingly, one of ordinary skill in the art would not reasonably be apprised of the metes and bounds of the invention.

Conclusion

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is

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(703) 305-3008. The examiner can normally be reached on Monday-Thursday, alternate Fridays, 8:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
August 25, 2001

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

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Interview Summary	Application No. 09/546,573	Applicant(s) HOLTEN-ANDERSEN ET AL.	
	Examiner Stephen L. Rawlings, Ph.D.	Art Unit 1642	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Stephen L. Rawlings, Ph.D.*. (3)_____.

(2) *Stanislaus Aksman*. (4)_____.

Date of Interview: *18 July 2001* .

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☐ No.
If Yes, brief description: _____ .

Claim(s) discussed: _____ .

Identification of prior art discussed: _____ .

Agreement with respect to the claims f)☐ was reached. g)☐ was not reached. h)☒ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *See Continuation Sheet* .

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

i)☒ It is not necessary for applicant to provide a separate record of the substance of the interview(if box is checked).

Unless the paragraph above has been checked, THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

_____
Examiner's signature, if required

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mary of Record of Interview Requiremen

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)
In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case unless both applicant and examiner agree that the examiner will record same. Where the examiner agrees to record the substance of the interview, or when it is adequately recorded on the Form or in an attachment to the Form, the examiner should check the appropriate box at the bottom of the Form which informs the applicant that the submission of a separate record of the substance of the interview as a supplement to the Form is not required.

It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

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Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: Mr. Acksman and I discussed the fact that a power of attorney and a change of address would need to be filed. Mr. Acksman and I also discussed the need to file a supplemental Form 892 independently citing the references cited in the International Search Report for the PCT case, to which the instant application claims benefit, and the need to submit copies of these references with the supplemental Form 892. Finally, Mr. Acksman and I discussed whether the requirements for the claim to foreign priority have been met. I affirmed that the requirements for foreign priority under 35 USC 119 (a-d) have been met.

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